

AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning on page 3, line 23 with the following paragraph.

-- Cystic fibrosis (CF) is an example of a genetic disease that is caused, individually or collectively, by any of a number of different mutations. Cystic fibrosis afflicts approximately 30,000 children and adults in the United States; afflicted patients typically die in their thirties. One in 31 Americans (one in 28 Caucasians) – more than 10 million people – is an unknowing, symptom-free carrier of a mutation that leads to the disease. An afflicted patient must have inherited two defective copies of a specific gene – one from each parent – to have CF. Each time two CF carriers conceive a child, there is a 25 percent chance that the child will have CF, a 50 percent ~~change~~ chance that the child will be an asymptomatic carrier; and a 25 percent chance that the child will be a non-carrier. --

Please replace the paragraph beginning on page 4, line 30 with the following paragraph.

-- In such situations, the design of the assay and methodology that efficiently achieves the goals described above is critical. Specifically, the assay must be rapid, accurate, and cost effective such that the assay can be performed as a routine part of patient care thereby expanding the utility of the assay from diagnosing individual patients to screening entire groups. The assay should be able to rapidly test multiple patient samples and be flexible enough to selectively recognize predominant mutations or markers for a disease. Through the ability to screen and identify a large number of genetic polymorphisms, the assay could both diagnose disease as well as yield epidemiological data about the prevalence of specific polymorphisms and the relation to the existence or severity of a condition that may ~~be~~ be correlated to a specific disease or that exists in a number of pathologies. Because many diseases have underlying genetic markers that have been identified and localized to identified regions of a patient's DNA that can be analyzed, once the specific genetic markers are identified, any number of diseases can be analyzed using the same assay format by simply altering the gene specific reagents in the assay that hybridize

with a patient's DNA to detect the known marker and correlating the presence of the marker with one or more diseases. Accordingly, once the assay design and methodology are realized, one additional disease, a group of diseases, or a group of polymorphisms that are directly or indirectly correlated to several diseases, can be detected with the assay format. As the genetic bases of other diseases are discovered, the gene specific assay reagents are readily modified to take advantage of the existing format to detect and analyze new diseases. For example, while cystic fibrosis is susceptible of detection by screening an identification of a discrete set of markers or mutations that are known to contribute to the disease, in other circumstances, the screening process may identify other polymorphisms that are not directly related to a single disease, but that are related to multiple diseases or that accompany different conditions such as a panel of diseases that may affect a certain population group. --

Please replace the paragraph beginning on page 8, line 14 with the following paragraph.

-- The preferred methodologies of the invention feature the advantageous use of the blocker sequences to separate and distinguish selected subsets of markers, wild type and mutant discriminator probes selectively detect the presence and/or identity of members of the known set of mutations, and universal reporters have labels that generate a signal upon hybridization with a common sequence of either the mutant or wild-type discriminator probes. In one embodiment of the invention, amplification products of a single patient are electronically addressed to a number of predetermined specific microlocations or on a microchip. As part of a screening step, different mixtures or groups of blockers specifically hybridize with identified loci of the amplicons. Loci that are not blocked hybridize with mutant or wild-type discriminator probes. By selecting mixtures of blocker sequences that are complementary to the identified loci of different subsets of the set of known markers, the detection of specific subsets can be localized at specific test sites for a specific patient. The reaction each discriminator probe generates a discrete signal that is detected by a signal detection and processing apparatus. Detection and signal processing steps distinguish the labels attached to mutant ~~verses~~ versus wild-type

discriminator probes, subtract background signal, and generate a signal or report that identifies the assay results for a particular patient. --

Please replace the paragraph beginning on page 9, line 20 with the following paragraph.

-- In CF for example, in the first set of hybridization reactions comprising the screening run, the assay may test for a total of 25 markers by testing, for example, a subset of between one and five mutations at each test site. In this example, the set of markers is comprised of 25 mutations or polymorphisms with a single predominant mutations and the amplicons from a single patient sample may be addressed to each of six test sites. One test site may be used for the predominant mutation, such that a group of 24 species of blocker sequences is introduced to the site to interrogate only the one remaining marker. At one other test site, blockers may block 20 of the identified loci and the remaining five markers are interrogated. Four other test sites are used analogously with different groups of blockers such that each marker is interrogated at one of the test sites. Because the predominant marker is interrogated individually at a dedicated test site, if the test site dedicated to the predominant marker tests positive, then the final result for that marker is achieved. If one of the other test sites generates a positive signal, the assay indicates that a member of a first subset, i.e. one or more of the markers interrogated at the site is present. Because more than one marker was interrogated at the test site, a subsequent set of reactions is required to distinguish which one or more of the five possible mutations is present. By removing the blockers and discriminators that were applied in the first hybridization reaction, a second set of blocker sequences can be applied to discriminate between the members of the subset of known mutations identified in the first reaction. The second set of hybridization reactions separates the members of the group of five identified in the first set by applying a second group of blockers that separate and distinguish the individual members of the subset. In this example, the second group of blockers is introduced to the test sites such that one test site interrogates one of the 5 members of the first subset identified in the screening run. Thus, the subsequent application of selected blocker groups identifies the individual within the subset identified in the screening step. In an alternative embodiment, the screening run may be skipped

and only the genotyping ~~[[runds]]~~ runs may be performed. Preferably, the genotyping runs are performed on an array containing 400 individually-addressable sites or microlocations. The reaction of a universal reporter generates the signal, as above, and the identity of the mutation is indicated by the specific test site at which signal is generated. The example of cystic fibrosis is an embodiment of the invention where a defined group of markers is directly correlated to a particular disease. Because the invention provides the ability to detect a very large number of mutations, substantially larger than the 25 mutations detected for CF, the invention can be used to screen patient DNA samples for dozens of mutations that may directly or indirectly correlate to a number of diseases or which may be identified as accompanying other mutations that are associated with a disease or are of other clinical or research interest. As will be appreciated from the description of the invention, the assay is capable of generating a signal for the presence of a heterozygous mutation as well as a homozygous mutation. As described above in the context of cystic fibrosis, the presence of a heterozygous mutation may indicate the carrier of a disease while the presence of a homozygous mutation may indicate the symptomatic presence of the disease. Because the detection of a heterozygous mutation will inherently generate a different signal than the presence of the homozygous mutation, the assay methodology and apparatus distinguishes between a heterozygous and homozygous mutation. For example, when the first universal reporter hybridizes with a mutant discriminator probe, the signal generated by the label of the first universal reporter is different than the signal generated by a second universal reporter that hybridizes with a wild-type discriminator probe. Where no mutation is present, mutant discriminator will not be bound and the signal will be generated by the second universal reporter binding to wild-type discriminator probes. For a heterozygous mutation, a signal will be generated by a universal reporter binding to both a wild-type discriminator probe and a mutant discriminator probe. For a homozygous mutation, wild-type discriminator will not be bound and the signal generated will be from a universal reporter binding to both mutant discriminator probes. The detection and data processing components of the invention process these results by establishing parameters that separate signal from noise for each of the three possibilities outlined above, as well as establishing a heterozygous ratio reference to utilize the signal generated by two different species of label that result from the binding of two different universal reporters. To

facilitate both qualitative and quantitative analysis of the various reactions described herein, the apparatus also employs reference and control reactions to ensure that the mutation detection functions are valid. --

Please replace the paragraph beginning on page 29, line 30 with the following paragraph.

-- Mutant discriminators that are selected for each polymorphism are then loaded onto the microchip device under stringent conditions conducive to selective hybridization of discriminator probes to the amplicons. In a preferred embodiment, discriminator probes are hybridized by a touch down thermal method in which the microchip device is heated before and for a short period after the discriminator probes are added and then the temperature is slowly decreased. These temperature changes are followed by or performed in conjunction with several high salt washes to further increase specificity of the discriminator probe binding. In another preferred embodiment, discriminators are hybridized using non-stringent conditions such that both wild-type and mutant signals are approximately equal. Following hybridization, discrimination occurs using thermal, chemical, or e-stripping, leaving only matched signals. --

Please replace the paragraph beginning on page 39, line 17 with the following paragraph.

-- For all of the test sites for which useful signal is generated, the adjusted signal from each test site is calibrated using a multiplier calculated from the signal from the test site with the corresponding heterozygous ratio reference (i.e., the heterozygous ~~ratio~~ ratio reference that contains the same sequence as the variant being queried at a particular test site ~~a suite~~). In a preferred embodiment, in which a first label corresponds to the wild-type and second label to the polymorphism, a label one/label two scale factor, which will be referred to as a "multiplier," is calculated from each group of heterozygous ratio references. This multiplier adjusts the lower of the label one or label two signals that correspond to the ratio references in such a way that after adjustment the signal from the wild-type ratio reference equals the signal from the mutant ratio reference. --

Please replace Table 1, beginning on page 37, line 4 with the following table.

| Test Site | Genotyping Pad 1 | Genotyping Pad 2 | Genotyping Pad 3 | Genotyping Pad 4 | Genotyping Pad 5 |
|--------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| Screening Pad 1 | A | B | C | D | E |
| Screening Pad 2 | F | G | H | I | J |
| Screening Pad 3 | K | L | M | N | O |
| Screening Pad 4 | P | Q | R | S | T |
| Screening Pad 5 | U | V | W | X | Y |

Please replace Table 2, beginning on page 46, line 1 with the following table.

| Mutation | Relevant References |
|----------------|--|
| G 85 E | Tsui 6,001,588 |
| R 117 H | (1990) Dean, M, <i>Cell</i> 61:863-870 |
| I 148 T | (1994) Bozon D, <i>Hum. Mut.</i> 3:330-332 |
| R 334 W | (1991) Gasparini P, <i>Genomics</i> , 10:193-200 |
| R 347 P | (1990) Dean, M, <i>Cell</i> 61:863-870 |
| A 455 E | Tsui 6,001,588 |
| Δ F 508 | Tsui 5, 776,677 |
| Δ I 507 | Tsui 6,001,588 |
| G 542 X | Tsui 6,001,588 |
| G 551 D | Cutting 5,407,796 |
| R 553 X | Cutting 5,407,796 |
| R 560 T | Tsui 6,001,588 |

| | |
|---------------|--|
| R 1162 X | (1991) Gasparini P, <i>Genomics</i> , 10:193-200 |
| W 1282 X | (1990) Vidaud M, <i>Hum Genet.</i> , 85:446-449 |
| N 1303 K | (1991) Osborne L, <i>Am J. Hum Genet.</i> 48: 608-612 |
| 621 +1G→T | Tsui 6,001,588 |
| 711 +1G→T | Tsui 6,001,588 |
| 1078 delT | (1992) Claustres M <i>Genomics</i> , 13:907-908 |
| 1717 -1G→A | Tsui 6,001,588 |
| 1898 +1G→A | (1990) Guillermit H <i>Hum Genet.</i> 85(4):450-453 |
| 2184 delA | 2183 AA → G (1994) Bozon D, <i>Hum. Mut.</i> 3:330-332 |
| 2789 +5G→A | (1993) Ferec C <i>Hum Mol. Genet.</i> 2(10):1557-60 |
| 3120 +1G→A | (1996) Bienvenu <i>Hum Hered</i> 46(3):168-71 |
| 3659 delC | Tsui 6,001,588 |
| 3849 +10kbC→T | (1994) Highsmith WE, <i>New Engl. J Med.</i> 331:974-980 |
| Reflex test | |
| 5T/7T/9T* | (1997) Friedman KJ <i>Hum Mut</i> 10:108-115 |

Please replace Table 5, beginning on page 50, line 2 with the following table.

| | |
|------------|---|
| 1. Exon 11 | 5'biotin-TCAACTGTGGTTAAAGCAATAGTGTGATA-3' <u>SEQ ID NO: 1</u> |
| 2. Exon 4 | 5'biotin-TTTATCCCTTACTTGTACCAGCTCACTACCTAA-3' <u>SEQ ID NO: 2</u> |
| 3. Exon 21 | 5'biotin-TTCACAAGGGACTCCAAATATTGCTGTAG-3' <u>SEQ ID NO: 3</u> |
| 4. Exon 7 | 5'biotin-ATTATGGTACATTACCTGTATTTGTTTATTG3' <u>SEQ ID NO: 4</u> |
| 5. Exon 10 | 5'biotin-GATGGGTTTTATTTCCAGACTTCACTTCTAATG3' <u>SEQ ID NO: 5</u> |
| 6. Exon 19 | 5'biotin-AATTGTGAAATTGTCTGCCATTCTT3' <u>SEQ ID NO: 6</u> |
| 7. Exon 16 | 5'biotin-GATATAGCAATTTTGATGACCTTCTG3' <u>SEQ ID NO: 7</u> |
| 8. Exon 20 | 5'biotin-AATATAATTTAGTTGCCTTTTTCTGGCTAAGTCC3' <u>SEQ ID NO: 8</u> |
| 9. Exon 12 | 5'biotin-TCAAGAGGTAAAATGCAATCTATGATG3' <u>SEQ ID NO: 9</u> |

| | |
|---------------|--|
| 10. Exon 13 | 5'biotin-TGTCTGTAACTGATGGCTAACAAAATA3' <u>SEQ ID NO: 10</u> |
| 11. Exon 14b | 5'biotin-CACTACCATAATGCTTGGGAGAAAT3' <u>SEQ ID NO: 11</u> |
| 12. Exon 3 | 5'biotin-ATGCAACTTATTGGTCCCACTTTTT3' <u>SEQ ID NO: 12</u> |
| 13. Exon 5 | 5'biotin-TGTCAAGCCGTGTTCTAGATAAAATAAG3' <u>SEQ ID NO: 13</u> |
| 14. Intron 19 | 5'biotin-GTTAAACAGTGTTGAATTTGGTGCTA3' <u>SEQ ID NO: 14</u> |
| 15. Exon 9 | 5'biotin-AAGAACTACCTTGCTGCTCCAG3' <u>SEQ ID NO: 15</u> |

Please replace Table 6, beginning on page 50, line 6, with the following table.

| | |
|---------------|--|
| 1. Exon 11 | 5'CAGAAACAGAATATAAAGCAATAGAGAAATG3' <u>SEQ ID NO: 16</u> |
| 2. Exon 4 | 5'TCACCAAAGCAGTACAGCCTCTCTTA3' <u>SEQ ID NO: 17</u> |
| 3. Exon 21 | 5'CCATATTTCTTGATCACTCCACTGTT3' <u>SEQ ID NO: 18</u> |
| 4. Exon 7 | 5'CAGAACTGAACTGACTCGGAAGG3' <u>SEQ ID NO: 19</u> |
| 5. Exon 10 | 5'ATATAATTTGGGTAGTGTGAAGGGTT3' <u>SEQ ID NO: 20</u> |
| 6. Exon 19 | 5'CCCTGAGGGCCAGATGTCA3' <u>SEQ ID NO: 21</u> |
| 7. Exon 20 | 5'CCTATATGTCACAGAAGTGATCCCATC3' <u>SEQ ID NO: 22</u> |
| 8. Exon 12 | 5'GAACTGTTTAAGGCAAATCATCTACAC3' <u>SEQ ID NO: 23</u> |
| 9. Exon 13 | 5'TTCCCCAACTCTCCAGTCT3' <u>SEQ ID NO: 24</u> |
| 10. Exon 14b | 5'AGGTGAAGATGTTAGAAAAAAATCAACT3' <u>SEQ ID NO: 25</u> |
| 11. Exon 3 | 5'CACAAAAATGCATATAGTTATGTGATACA3' <u>SEQ ID NO: 26</u> |
| 12. Exon 5 | 5'AACTCCGCCTTTCAGTTGTATAAT3' <u>SEQ ID NO: 27</u> |
| 13. Intron 19 | 5'GACTTGTCATCTTGATTCTGGAGAC3' <u>SEQ ID NO: 28</u> |
| 14. Exon 9 | 5'AGATCATGTCCTCTAGAAACCGTATGCTATA3' <u>SEQ ID NO: 29</u> |
| 15. Exon 16 | 5'TCACATTTGCTTTTGTATTGTTTTTTTA3' <u>SEQ ID NO: 30</u> |

Please replace Table 7, beginning on page 52, line 13, with the following table.

| Well | Reagent | Description of Reagent |
|------|------------------|---|
| 1 | Blocker Group A1 | All blocked except 621+1(G>T), G542X, 1898+1(G>A), 2184delA, 3849+10kb(C>T) |
| 2 | Blocker Group A2 | All blocked except R334W, ΔI507, 1717-1(G>A), 3659delC, N1303K |
| 3 | Blocker Group A3 | All blocked except R117H, 1078delT, G551D, R1162X |

| | | |
|----|--|--|
| 4 | Blocker Group A4 | All blocked except G85E, I148T, 711+1 (G>T), A455E, R560T |
| 5 | Blocker Group A5 | All blocked except R347P, R553X, 2789+5 (G>A), 3120+1 (G>A), W1282X |
| 6 | Blocker Group A6 | All blocked except ΔF508 |
| 7 | ΔF508 Ratio Reference & T-tract Ratio References | |
| 8 | Empty | |
| 9 | ¼ low salt buffer | |
| 10 | ¼ low salt buffer | |

Please replace Table 8, beginning on page 53, line 23, with the following table.

| | |
|---------------------------|--|
| Universal Reporter, Red | 5' ctcaatgttcggactcag-Alexa Fluor 532-3' <u>SEQ ID NO: 31</u> |
| Universal Reporter, Green | 5' tgtcaagcgatatactgc-Alexa Fluor 647-3' <u>SEQ ID NO: 32</u> |

Please replace the paragraph beginning on page 63, line 3, with the following paragraph.

The reader increased the temperature of the chip to 56 °C for 60 ~~second~~ seconds, decreased the temperature to 42 °C for 30 seconds, performed 8 high salt washes, and lowered the temperature to 24 °C. Then, the reader performed discriminator scans (to detect red and green label) of the test sites with the samples, the test site with the histidine background, and the microlocations with the heterozygous ratio references, offloading this data to the computer system. The reader then increased the temperature of the chip to 56 °C for 60 seconds, performed four high salt washes of the chip to denature the discriminators and lowered the temperature of the chip to 24 °C. Then, it ejected the microchip that was analyzed, displaying a

“complete” icon next to that protocol. If more than one screening variant group was identified as containing a mutation in the screening run, the user selected another protocol to run, and the ASM again prompted the user as to which microchip and genotyping reporter mix to use. This process was repeated until all of the necessary protocols had been run.

Please replace the paragraph beginning on page 64, line 27, with the following paragraph.

-- The reader increased the temperature to 56 °C for 60 second, decreased temperature to 38 °C for 30 seconds, performed eight low salt washes, and decreased temperature to 24 °C. Then, the reader performed a red/green scan of test site 6, the background control test site, and the T-tract heterozygous ratio reference test site, which was addressed with the dF508 heterozygous ratio reference during the screening run. The data collected was offloaded to the PC. After the scan the reader increased the temperature of the chip to 56 °C, performed four low salt washes, and then set the temperature at 24 °C. --

Please replace Table 11, beginning on page 68, line 2, with the following table.

| Discriminator for: | Sequence |
|------------------------------|---|
| dI507, Wild-type | 5'aagatgatattttcttaactgagtcggaacattgag3' <u>SEQ ID NO: 33</u> |
| Screening, dI507 Mutant | 5'aaagatattttcttaattgcagtatatcgcttgaca3' <u>SEQ ID NO: 34</u> |
| dI507, Mutant | 5'aaagatattttcttaatggcagtatatcgcttgaca3' <u>SEQ ID NO: 35</u> |
| I507V, Mutant | 5'aagacgatattttcttaactgagtcggaacattgag3' <u>SEQ ID NO: 36</u> |
| I506V, Mutant | 5'aagatgacattttcttaactgagtcggaacattgag3' <u>SEQ ID NO: 37</u> |
| F508C, Mutant | 5'ctgagtcggaacattgagggaacaccacaga3' <u>SEQ ID NO: 38</u> |
| 1717-1, Wild type | 5'ctgagtcggaacattgaggatgtcttattacc3' <u>SEQ ID NO: 39</u> |
| 1717-1, Mutant | 5'gcagtatatcgcttgacagatgtcttattacc3' <u>SEQ ID NO: 40</u> |
| Screening, 1717-1, mutant | 5'gcagtatatcgcttgacaagatgtcttattacc3' <u>SEQ ID NO: 41</u> |
| 3659delC, Wild-type | 5'ctgagtcggaacattgagttgacttgtaggt3' <u>SEQ ID NO: 42</u> |

| | |
|-----------------------------|---|
| Screening 3659delC, Mutant | 5'gcagtatatcgcttgacattgactgttaggtt3' SEQ ID NO: 43 |
| 3659delC, Mutant | 5'gcagtatatcgcttgacattgactgttaggtt3' SEQ ID NO: 44 |
| G542X, Wild-type | 5'ctgagtccgaacattgagcttctccaagaact-3' SEQ ID NO: 45 |
| G542X, Mutant | 5'gcagtatatcgcttgacaccttctcaaagaac-3' SEQ ID NO: 46 |
| R553X, Wild-type | 5'ctgagtccgaacattgagtgctcgttgacc3' SEQ ID NO: 47 |
| R553X, Mutant | 5'gcagtatatcgcttgacattgctcattgacct3' SEQ ID NO: 48 |
| Screening R553X, Mutant | 5'gcagtatatcgcttgacataattcttgctca' SEQ ID NO: 49 |
| G85E, Wild-type | 5'ctgagtccgaacattgagagattccatagaac3' SEQ ID NO: 50 |
| G85E, Mutant | 5'gcagtatatcgcttgacaaagatttcatagaac3' SEQ ID NO: 51 |
| I148T, Wild-type | 5'ctgagtccgaacattgagcatcacattggaatg' SEQ ID NO: 52 |
| I148T, Mutant | 5'gcagtatatcgcttgacaatcacactggaatg3' SEQ ID NO: 53 |
| R117H, Wild-type | 5'ctgagtccgaacattgagggaacgctctatc3' SEQ ID NO: 54 |
| R117H, Mutant | 5'gcagtatatcgcttgacaggaacactctatcg3' SEQ ID NO: 55 |
| 711+1, Wild-type | 5'ctgagtccgaacattgagggtacatacttcatc3' SEQ ID NO: 56 |
| 711+1, Mutant | 5'gcagtatatcgcttgacaaggtacataattcat3' SEQ ID NO: 57 |
| R334W, Wild type | 5'ctgagtccgaacattgagcatcctccgaaaa3' SEQ ID NO: 58 |
| R334W, Mutant | 5'gcagtatatcgcttgacacatcctctgaaaa3' SEQ ID NO: 59 |
| 1078delT, Wild-type | 5'ctgagtccgaacattgaggttctttgtggtgt3' SEQ ID NO: 60 |
| 1078delT, Mutant | 5'gcagtatatcgcttgacagttcttgtggtgt3' SEQ ID NO: 61 |
| Screening, 1078delT, Mutant | 5'gcagtatatcgcttgacagttcttgtggtgt3' SEQ ID NO: 62 |
| A455E, Wild type | 5'ctgagtccgaacattgagtgcggttgct3' SEQ ID NO: 63 |
| A455E, Mutant | 5'gcagtatatcgcttgacattggaggttgct3' SEQ ID NO: 64 |
| Δ508, Wild type | 5'ctgagtccgaacattgaggaaacaccaaaga3' SEQ ID NO: 65 |
| Δ508, Mutant | 5'gcagtatatcgcttgacaataggaaacaccgat3' SEQ ID NO: 66 |
| G551D, Wild type | 5'ctgagtccgaacattgagcgttgacctccac3' SEQ ID NO: 67 |
| G551D, Mutant | 5'gcagtatatcgcttgacacgttgatctccact3' SEQ ID NO: 68 |
| Screening G551D, Mutant | 5'tctccactcagttgcagtatatcgcttgaca3' SEQ ID NO: 69 |
| R560T, Wild type | 5'ctgagtccgaacattgagtattcaccttgcta3' SEQ ID NO: 70 |
| R560T, Mutant | 5'gcagtatatcgcttgacaattcacgttgcta3' SEQ ID NO: 71 |
| 2184delA, Wild-type | 5'ctgagtccgaacattgagattgtttttgtttc3' SEQ ID NO: 72 |

| | |
|---------------------------------|--|
| 2184delA , Mutant | 5'gcagtatatcgcttgacaattgttttct3' <u>SEQ ID NO: 73</u> |
| 2789+5, Wild type | 5'ctgagtcggaacattgagaagtgagattcc3' <u>SEQ ID NO: 74</u> |
| 2789+5 , Mutant | 5'gcagtatatcgcttgacaaaagtgaattcca3' <u>SEQ ID NO: 75</u> |
| 3120+1, Wild type | 5'ctgagtcggaacattgagacataacctggatg3' <u>SEQ ID NO: 76</u> |
| 3120+1 Mutant | 5' - gcagtatatcgcttgacaacatatctggatg - 3' <u>SEQ ID NO: 77</u> |
| R1162, Wild type | 5'ctgagtcggaacattgagctcggtcaca3' <u>SEQ ID NO: 78</u> |
| R1162 , Mutant | 5'gcagtatatcgcttgacagactcagctcaca3' <u>SEQ ID NO: 79</u> |
| N1303K, Wild type | 5'ctgagtcggaacattgagatccaagtttt3' <u>SEQ ID NO: 80</u> |
| N1303K , Mutant | 5'gcagtatatcgcttgacaatccaacttttc3' <u>SEQ ID NO: 81</u> |
| R347P, Wild type | 5'ctgagtcggaacattgagcattgttctcg3' <u>SEQ ID NO: 82</u> |
| R347P , Mutant | 5'gcagtatatcgcttgacaattgttctgcc3' <u>SEQ ID NO: 83</u> |
| Stabilizer, R347P | 5'catggcggtcactcggaatttcctg3' <u>SEQ ID NO: 84</u> |
| 1898+1, Wild type | 5' - ctgagtcggaacattgagtgaaggtatgttc -3' <u>SEQ ID NO: 85</u> |
| 1898+1 , Mutant | 5'gcagtatatcgcttgacattgaaagatatgttct3' <u>SEQ ID NO: 86</u> |
| 621+1 Wild type | 5' ctgagtcggaacattgagataagaagtaatac 3' <u>SEQ ID NO: 87</u> |
| 621+1 , Mutant | 5' gcagtatatcgcttgacataaagaagtaatact 3' <u>SEQ ID NO: 88</u> |
| W1282X, Wild type | 5'ctgagtcggaacattgagacagtggaggaaa3' <u>SEQ ID NO: 89</u> |
| W1282X , Mutant | 5'gcagtatatcgcttgacaacagtgaaggaaa3' <u>SEQ ID NO: 90</u> |
| 3849+10kb, Wild type | 5'ctgagtcggaacattgagaaatggcgagta3' <u>SEQ ID NO: 91</u> |
| 3849+10kb, Mutant | 5'gcagtatatcgcttgacaaaaatggtgagtaa3' <u>SEQ ID NO: 92</u> |
| T-tract, 5T | 5'ctgagtcggaacattgagtgtgttttaacagg3' <u>SEQ ID NO: 93</u> |
| T-tract, 7T | 5'gcagtatatcgcttgacatgtgttttttaacagg3' <u>SEQ ID NO: 94</u> |
| T-tract, 9T | 5'gcagtatatcgcttgacatgtgttttttaacagg3' <u>SEQ ID NO: 95</u> |
| Amplicon Confirmation, Exon 12 | 5'gcagtatatcgcttgacatgaaaggtatgttc3' <u>SEQ ID NO: 96</u> |
| Amplicon Confirmation, Exon 21 | 5'gcagtatatcgcttgacagatccaagtttt3' <u>SEQ ID NO: 97</u> |
| Amplicon Confirmation, Exon 7 | 5'gcagtatatcgcttgacaGTTCTTTGTGGTGT3' <u>SEQ ID NO: 98</u> |
| Amplicon Confirmation, Exon 9 | 5'gcagtatatcgcttgacaTGGCGGTTGC3' <u>SEQ ID NO: 99</u> |
| Amplicon Confirmation, Exon 14b | 5'gcagtatatcgcttgacaAaagtgagattcc3' <u>SEQ ID NO: 100</u> |

Please replace Table 12, beginning on page 70, line 2, with the following table.

| Blocker | Sequence |
|---------------------------------|--|
| 3849+10kb Blocker | 5'gttcagcattataaaatggygagtaagacaccctgaaaggaaatgttctattcatgg3' SEQ ID NO: 101 |
| Δ507 Blocker screening run | 5'gatattttctttaatggtgccaggcataatccaggaaaactgagaacagaatg3' SEQ ID NO: 102 |
| Δ508 Blocker screening run | 5'tgctttgatgacgcttctgtatctatattcatcataggaacacc3' SEQ ID NO: 103 |
| Δ507/Δ508 wild- type Blocker | 5'tattcatcataggaacaccaaagatgatattttctttaatggtg3' SEQ ID NO: 104 |
| Δ507 Blocker, mutant | 5'ctatattcatcataggaacaccaaagatattttctttaatggtg3' SEQ ID NO: 105 |
| Δ508 Blocker, mutant | 5'ctatattcatcataggaacaccgatgatattttctttaatggtg3' SEQ ID NO: 106 |
| 621+1 Blocker | 5'tatgttttagtttgattataagaagktaatacttccttgacaggcccatggcacata3' SEQ ID NO: 107 |
| 2184DelA Blocker Wild type | 5'gtctgtttaaaagattgtttttgttctgtccaggag3' SEQ ID NO: 108 |
| 2184DelA Blocker Mutant | 5'gtctgtttaaaagattgtttttgttctgtccaggag3' SEQ ID NO: 109 |
| 1898+1 Blocker | 5'gatgttttaacagaaaaagaaatattgaaagrtatgttcttgaataccttact3' SEQ ID NO: 110 |
| N1303K Blocker | 5'cactgttcattaggatccaastttttctaaatgtccag3' SEQ ID NO: 111 |
| W1282X Blocker | 5'caataactttgcaacagtgraggaaagcctttggagtataccac3' SEQ ID NO: 112 |
| 711+1 Blocker | 5'gtgcctaaaagattaaatcaataggtacatamttcatcaaatgttc3' SEQ ID NO: 113 |
| R117H Blocker | 5'cggataacaaggaggaacrtctatcgcatattatctaggc3' SEQ ID NO: 114 |
| I148T Blocker | 5'gccattttggccttcacacaytggaatgcagatgagaatagc3' SEQ ID NO: 115 |
| G85E Blocker | 5'ccttaccctaaatataaaaagattycatagaacataaatctcc3' SEQ ID NO: 116 |
| I162 Blocker | 5'caatgaacttaagactcrgctcacagatcgcatctgaaataaaaa3' SEQ ID NO: 117 |
| 3659DelC Blocker Wild Type | 5'gtatggtttggttgacttgtaggtttaccttctg3' SEQ ID NO: 118 |
| 3659DelC Blocker Mutant | 5'gtatggtttggttgacttgtaggtttaccttctg3' SEQ ID NO: 119 |
| 3120+1Blocker | 5'cggctactattttacataYctggatgaagcaaatatggttaaga3' SEQ ID NO: 120 |
| 2789+5 Blocker | 5'-gtgctgtggctccttgaaagtartattccatgtcctattgtgtagattgtg-3' SEQ ID NO: 121 |
| A455E Blocker | 5'gaggacagtgttggmggttgctggatccactggagcaggcaagg3' SEQ ID NO: 122 |

| | |
|-------------------------------|---|
| R334W Blocker | 5'ctaataaaaggaatcatcctcyggaaaatattcaccaccatctca3' <u>SEQ ID NO: 123</u> |
| 1078DelT Blocker Wild Type | 5'gctcagccttcttctctcagggttcttggtgttttatctg3' <u>SEQ ID NO: 124</u> |
| 1078DelT Blocker Mutant | 5'gctcagccttcttctctcagggttcttggtgttttatctg3' <u>SEQ ID NO: 125</u> |
| R347P Blocker | 5'ttctgcattgttctgcscatggcggtcactcggcaattccctgggctgta3' <u>SEQ ID NO: 126</u> |
| 1717-1 Blocker | 5'gagatgtcytattacaaaaatagaaaattagagagtcac3' <u>SEQ ID NO: 127</u> |
| G542X Genotyping Blocker | 5'actttctcmaagaactatattgtcttctctgcaaactg3' <u>SEQ ID NO: 128</u> |
| G551D Screening Blocker | 5'ttgacctccactcagtggtattccaccttctccaac3' <u>SEQ ID NO: 129</u> |
| G551D/R553X/R56 0T Blocker | 5'-tat tca cct tgc taa aga aat tct tgc tgc ttg acc tcc act-3' <u>SEQ ID NO: 130</u> |
| G542X/G551D/R55 3X Blocker | 5'-ttg ctc gtt gac ctc cac tca gtg tga ttc cac ctt ctc caa gaa cta ta-3' <u>SEQ ID NO: 131</u> |
| R553/X Blocker | 5'caataattagttattcaccttgctaaagaaattcttgcctgga3' <u>SEQ ID NO: 132</u> |
| R560T Blocker | 5'cttgctagaccaataattagttattcacyttgcta3' <u>SEQ ID NO: 133</u> |